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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,796	DENNY ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment, which included amendment to claims 4, 6, 7, 10, 12, 15, 17, 18, 20, 21, 23, 26, 28, 30, 31, 33, 34 and 36, filed on 8/25/2006, is made of record. Claims 1-36 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 8/25/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Recitation of "one or more" 1,2,4-benzotriazine-1,4-dioxides in claim 1 renders claim 1 and its dependent claims 2-12 indefinite as it is not clear what is intended. Note 1,2,4-benzotriazine-1,4-dioxide is species and not a genus.

2. Claim 3 and its dependent claims 6-8 are improper dependent claim as claim 3 fails to limit the scope of claim 1 on which it is dependent. Claim 1 recites a single species while claim 3 includes several species of substituted benzotriazines. In addition claim 3 recites " and their pharmaceutically acceptable salts thereof' which is not in claim 1. Hence, scope of claim 3 is broader than the scope of claim1. Furthermore Markush choice stated in claim 3 should be in alternative and singular.

3. Claim 9 is an improper dependent claim as it recites a pharmaceutical composition while claim 2 is a method claim not a compound or composition. Claim 12 is also an improper dependent claim as it recites a pharmaceutical composition while claim 2 is a method claim not a compound or composition.

4. Claims 10, 11, 21, 22, 34 and 35 provide for the use of the compound recited in claim 2, 13 and 24 respectively but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

5. Recitation of "including" in claims 12 , 23 and 36, renders these claims indefinite as the transitional term "including" is open and implies more than what is being positively recited therein. See MPEP 2111.03 which states under transitional phrases The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495,501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

6. Claim 21 and its dependent claim 22 are indefinite as claim 21 recites "any claim 13". It is not clear what is intended.

7. Claim 24 and its dependent claims 25-36 are indefinite as it recites " a pharmacologically acceptable salt thereof" at two places. It is not clear what is intended.

8. Recitation of "other antimetabolites" in claim 8, 19 and 32 renders these claim vague and unclear as it is not clear what these antimetabolites are. Structural make-up of these antimetabolites remains unknown.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 15-22 and 28-35 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer, does not reasonably provide enablement for treating any or all cancers and solid tumors as generically embraced in the instant claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) level of skill in the art, 8) the quantity of experimentation needed.

1) The nature of the invention:

The instant method of use claims 4, 15 and 28 are drawn to therapy for cancers with various 1,2,4-benzotriaizne-1,4-oxides, claims 20 and 33 are drawn to radiosensitising of solid tumor in presence of various 1,2,4-benzotriaizne-1,4-oxides and claim 1 is drawn to indirectly treating cancer and radiosensitising of solid tumor.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of cell proliferation by cytotoxicity via hypoxia, by the instant compounds, instant claims reach through inhibiting and treating any or all cancers and tumors in general and thereby they lack adequate written description and enabling disclosure in the specification.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. Accordingly, treatments for cancer are normally tailored to the particular type of cancer present, as there is no, and there can be no “magic bullet” against cancer generally.

Thus, the scope of claim is extremely broad.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of cell proliferation by imparting cytotoxicity via hypoxia, based on limited

assay, it is claimed that treating any or all solid tumors or cancers in general, for which there is no enabling disclosure. The scope of the claims includes any or all cancer based on the mode of action of the compound of instant claims for which there are no enabling disclosure. In addition, the scope of these claims as recited would include treatment of various cancers such as lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification.

Moreover many if not most of diseases such as, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The instant compounds are disclosed to cell proliferation inhibitory activity by imparting cytotoxicity via hypoxia and it is recited that the instant compounds are therefore useful in treating any or all cancers and solid tumors stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cell proliferation inhibitor that would be useful for all sorts of proliferative diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

The scope of the invention includes large number of 1,2,4-benzotriazine-1,4-oxides compounds as well as the thousand and thousand of diseases embraced by the terms recited above.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “compound” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body.

Also see the PTO website

<<http ://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7>>

ENABLEMENT DECISION TREE, Example F, situation 1) which is directed to the scope of cancer.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is “speculative”, “sufficiently unusual” or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds.

2) The state of the prior art: The state of the art is indicative of the requirement for undue experimentation. See Bussink et al., Radiotherapy and Oncology, 67, 3-15, 2003. Especially see concluding paragraph. Since hypoxia inducing factor is associated with altered protein kinase activity, it is important to point out that that "there may be 2,000

protein kinases" (Cohen et al., The development and therapeutic potential of protein kinase inhibitors, page 459) and that "nearly all protein kinases belong to the same superfamily and it seemed unlikely that small cell-permeant molecules could be developed that would inhibit one kinase specifically without inhibition at least a few others" (Cohen et al., same paragraph). Therefore, there may be various possible adverse effects when a compound of formula (I) is given to a patient to treat any of the aforementioned diseases. Much experimentation and in vivo testing must be carried out to make sure that the administration of the compounds of formula (I) results in enhanced therapeutic effects without harmful side effects.

Hence, in the absence of showing of correlation between all the diseases claimed as capable of treatment with inhibition of altered protein kinase activity, one of skill in the art is unable to fully predict possible results from the administration of the compounds of formula (I) due to the unpredictability of the role of the instantly claimed compounds. For example, since it is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumor with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy.

Applicant's disclosure does not enable one of ordinary skill in the art to use the claimed invention within the entire scope of the diseases listed above. There is no compound, let alone an entire class of compounds that can treat the various and divergent diseases

listed above, as claimed. Cell proliferation by various mode of action is still exploratory and requires further experimentation.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney. (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences/n Vitro). Further, although drawn specifically to cancer cells, Dermer

(Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Applicants claim the treatment of various cancers. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancer have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al., page 531). Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art that the role of hypoxia in tumor biology

remains incompletely understood and inhibition of tumor cell proliferation by hypoxia of is still exploratory. It clear that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present:

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The only direction or guidance present in the specification is the listing of diseases applicant considers treatable. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art to extrapolate to the other compounds of the claims.

The disclosure does not provide how this in vitro data correlates to the treatment of the assorted diseases claimed. The instant specification is short of any examples or data in regards to the supposed treating of the aforementioned diseases. Applicants have not provided any competent evidence or disclosed tests that are highly predictive

for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

5) the presence or absence of working examples: Specification has no working examples to show treating all cancers including all solid tumors and the state of the art is that the effects of cell proliferation inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace a large genus of compounds and treatment of any or all solid tumors or cancers. For such a scope, there is no enabling disclosure in the specification.

7)The level of skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of the instant claims for the treatment of the various claimed diseases as a result necessitating one of skill to perform an exhaustive search for which disorders can be treated by what compounds of the instant claims in order to practice the claimed invention.

8) The quantity of experimentation: The quantity of experimentation needed is undue experimentation. It would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above. One of skill in the art would need to determine what diseases out of the multitude claimed would be benefited (i.e. treated) by the administration of the compounds of formula (I) and would furthermore have to determine which of the claimed compounds would provide treatment of which cancer or solid tumor.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to

engage in undue experimentation to test which diseases can be treated by the compounds encompassed in the instant claims, with no assurance of success.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10, 11, 21, 22, 34 and 35 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-25 and 27-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. WO 89/08647.

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula shown in page 4 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 4 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant compounds. See pages 4-8 for details of the invention. Especially see pages 8-11 for various compounds made.

Claims 1-25 and 27-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. WO 91/004028.

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula shown in page 5 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 5 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant compounds. See pages 5-14 for details of the invention. Especially see pages 14-22 for various compounds made.

Claims 2, 3, 13, 14 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by DD 272 591.

DD 272 591 teaches several 1,2,4-benzotriazine-1,4-dioxides as herbicides which include instant compounds. See formula I and note with the given definition of R^1,

R^2, R+3 and R^4 compounds taught in this document include instant compounds. See entire document. Especially see Table 1 for various compounds made.

Claims 1, 2, 4-12, 13, 15-24 and 28-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. EP 0649 658.

Brown teaches several 1,2,4-benzotriazine-1,4-dioxide of formula I, shown in page 2 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See formula I, page 2 and note with the given definition of x, y^1 and y^2, compounds taught by Brown include instant compounds. See pages 2-7 for details of the invention and pages 8-10 for process of making. Especially see pages 11-20 for Examples 1-10.

Claims 1-25 and 27-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. US 20020103200.

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula I shown in page 2 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 2 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant compounds. See pages 2-4 for details of the invention. Especially see pages 4-7 for various compounds made. Also see pages 7-9 for process of making and pages 9-15 for examples 1-15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al., WO 89/08647.

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula shown in page 4 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 4 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant compounds. See pages 4-8 for details of the invention. Especially see pages 8-11 for various compounds made.

Lee did not exemplify all compounds of formula shown in page 4 with various x, y^1 and y^2. However, Lee teaches equivalency of those compounds exemplified with those generically claimed. In addition, Lee provides adequate guidance to select various x, y^1 and y^2. Given the number of examples, there are only finite number possible compounds with the given choices of x, y^1 and y^2. For example, instant claim claims 6-methyl-1,2,4-benzotriazine-3-amine-1,4-dioxide. Lee teaches 1,2,4-benzotriazine-3-

amine-1,4-dioxide and it is within the skill set of one trained in the art to introduce a methyl in benzo ring. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula shown in page 4 with various x, y^1 and y^2 including instant compounds and expect them to have the use taught therein.

Also see KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. WO 91/004028.

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula shown in page 5 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 5 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant compounds. See pages 5-14 for details of the invention. Especially see pages 14-22 for various compounds made.

Lee did not exemplify all compounds of formula shown in page 5 with various x, y^1 and y^2. However, Lee teaches equivalency of those compounds exemplified with

those generically claimed. In addition, Lee provides adequate guidance to select various x, y^1 and y^2. Given the number of examples, there are only finite number possible compounds with the given choices of x, y^1 and y^2. For example, instant claim claims 6-methyl-1,2,4-benzotriazine-3-amine-1,4-dioxide. Lee teaches 1,2,4-benzotriazine-3-amine-1,4-dioxide and it is within the skill set of one trained in the art to introduce a methyl in benzo ring. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula shown in page 5 with various x, y^1 and y^2 including instant compounds and expect them to have the use taught therein.

Also see KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. US 20020103200 (or US 5,175,287)

Lee teaches several 1,2,4-benzotriazine-1,4-dioxide of formula I shown in page 2 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 2 and note with the given definition of x, y^1 and y^2, compounds taught by Lee include instant

compounds. See pages 2-4 for details of the invention. Especially see pages 4-7 for various compounds made. Also see pages 7-9 for process of making and pages 9-15 for examples 1-15.

Lee did not exemplify all compounds of formula shown in page 2 with various x, y^1 and y^2. However, Lee teaches equivalency of those compounds exemplified with those generically claimed. In addition, Lee provides adequate guidance to select various x, y^1 and y^2. Given the number of examples, there are only finite number possible compounds with the given choices of x, y^1 and y^2. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula shown in page 2 with various x, y^1 and y^2 including instant compounds and expect them to have the use taught therein.

Also see KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims.

Claims 2, 3, 13, 14 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over DD 272 591.

DD 272 591 teaches several 1,2,4-benzotriazine-1,4-dioxides as herbicides which include instant compounds. See formula I and note with the given definition of R^1, R^2, R^3 and R^4 compounds taught in this document include instant compounds. See entire document. Especially see Table 1 for various compounds made.

DD 272 591 did not exemplify all compounds of formula I with various R^1, R^2, R^3 and R^4. However, DD 272 591 teaches equivalency of those compounds exemplified with those generically claimed. In addition, DD 272 591 provides adequate guidance to select various R^1, R^2, R^3 and R^4. Given the number of examples, there are only finite number possible compounds with the given choices of R^1, R^2, R^3 and R^4. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula I with various R^1, R^2, R^3 and R^4 including instant compounds and expect them to have the use taught therein.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. WO 97/1699.

Brown teaches several 1,2,4-benzotriazine-1,4-dioxide of formula shown in page 5 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See page 1 and note with the given definition of x, y^1 and y^2, compounds taught by Brown include instant compounds. See pages 5-14 for details of the invention. Especially see pages 14-22 for various compounds made.

Brown did not exemplify all compounds of formula shown in page 5 with various x, y^1 and y^2. However, Brown teaches equivalency of those compounds exemplified with

those generically claimed. In addition, Brown provides adequate guidance to select various x, y^1 and y^2. And there are only finite number possible compounds with the given choices of x, y^1 and y^2. For example, instant claim claims 6-methyl-1,2,4-benzotriazine-3-amine-1,4-dioxide. Brown teaches 1,2,4-benzotriazine-3-amine-1,4-dioxide and it is within the skill set of one trained in the art to introduce a methyl in benzo ring. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula shown in page 5 with various x, y^1 and y^2 including instant compounds and expect them to have the use taught therein.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. EP 0649 658.

Brown teaches several 1,2,4-benzotriazine-1,4-dioxide of formula I, shown in page 2 for treating breast cancer by imparting hypoxia and for radiosensitising tumor cells, which include compounds generically claimed in the instant claims. See formula I, page 2 and note with the given definition of x, y^1 and y^2, compounds taught by Brown include instant compounds. See pages 2-7 for details of the invention and pages 8-10 for process of making. Especially see pages 11-20 for Examples 1-10.

Brown did not exemplify all compounds of formula shown in page 5 with various x, y^1 and y^2. However, Brown teaches equivalency of those compounds exemplified with those generically claimed. In addition, Brown provides adequate guidance to select various x, y^1 and y^2. And there are only finite number possible compounds with the given choices of x, y^1 and y^2. For example, instant claim claims 6-methyl-1,2,4-benzotriazine-3-amine-1,4-dioxide. Brown teaches 1,2,4-benzotriazine-3-amine-1,4-

dioxide and it is within the skill set of one trained in the art to introduce a methyl in benzo ring. Hence, it would be obvious to one trained in the art to make the compounds of the genus of formula shown in page 2 with various x, y^1 and y^2 including instant compounds and expect them to have the use taught therein.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624